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CLINICAL REVIEW
Clinical update

COVID-19: from epidemiology to treatment

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The COVID-19 pandemic has greatly impacted the daily clinical practice of cardiologists and cardiovascular surgeons. Preparedness of health workers and health services is crucial to tackle the enormous challenge posed by SARS-CoV-2 in wards, operating theatres, intensive care units, and interventionist laboratories. This Clinical Review provides an overview of COVID-19 and focuses on relevant aspects on prevention and management for specialists within the cardiovascular field.

Keywords COVID-19 • Coronavirus • Prevention • Treatment • Prognosis • Risk factors

Introduction and scope of the review

Case study 1: A 59-year-old male underwent cardiac surgery for complicated prosthetic valve endocarditis on 13 March. The following day, the referral hospital notified that the patient had been in contact for 24 h with a confirmed case of a COVID-19. A nasopharyngeal swab confirmed SARS-CoV-2 infection. The patient developed bilateral pneumonia with ARDS and died on March 20. The contact tracing revealed the patient had been in contact with 25 healthcare workers, one having become infected.

Takeaway: During the initial phases of the pandemic, while SARS-CoV-2 is actively circulating within the community and the healthcare system, systematic screening systematic screening for SARS-CoV-2 infection should be done in all transferred patients to avoid nosocomial transmission.

COVID-19 is an illness caused by a novel coronavirus initially called 2019-nCoV and currently named SARS-CoV-2. From December 2019 to date, COVID-19 has attained a global dimension, having been declared a pandemic by the World Health Organization (WHO) on 11 March 2020.[1] The outbreak started in the Chinese city of Wuhan, Hubei Province, allegedly in the Central Market, and rapidly spread. On 30 January the WHO declared the COVID-19 outbreak a global health emergency.[1] To date (May 5), >3.5 million SARS-CoV-2 infections and 250 000 deaths have been reported worldwide.[2] The pandemic has obliged many countries to enforce strict control measures. They include home quarantines, lockdowns, or severe limitations of air and road transport, telework, and others, which have a deep impact on the global economy and people's daily life and well-being. Moreover, COVID-19 has led to a large overload of health systems, especially at the hospital level, and has forced health authorities and healthcare professionals to rapidly adapt to a challenging and constantly changing situation. In some countries, hospitals have turned into virtually solely COVID-19 centres. A new disease far from being completely understood has totally challenged our institutions and put the function of cardiovascular services at stake.

In this Clinical Review, we aim to provide a comprehensive summary of the most relevant characteristics of SARS-COV-2 and

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One-sentence summary: This review provides an overview and practical guidance for cardiologists and cardiovascular surgeons on the prevention, diagnosis, treatment, and prognosis of COVID-19.

Table 1 Summary of the epidemiology of COVID-19 in the top 10 European countries

Country	No. of cases	No. of deaths	No. of patients recovered	Estimated cumulative incidence (non-standardized rate per 100 000 inhabitants)	Reported mortality (%)	Estimated total population infected [mean (95% CI)][5]
Spain	217 466	25 264	118 902	465.1	11.6	15% (3.7–41%)
Italy	210 717	28 884	81 654	348.5	13.7	9.8% (3.2–26%)
UK	187 842	28 446	902	276.7	15.1	2.7% (1.2–5.4%)
France	168 925	24 864	50 885	258.8	14.7	3.0% (1.1–7.4%)
Germany	165 745	6866	132 700	197.8	4.1	0.72% (0.28–1.8%)
Belgium	50 267	7924	12 378	433.7	15.8	3.2% (1.3–7.6%)
Netherlands	40 968	5082	322	239.1	12.4	3.7% (1.3–9.7%)
Switzerland	29 981	1762	24 500	346.4	5.9	–
Portugal	25 524	1063	1712	250.3	4.2	1.1% (0.36–3.1%)
Ireland	21 506	1303	13 386	435.5	6.0	–
Total	1 118 941	131 458	321 507	–	11.7	–

Incidence estimates are calculated based on current population data from each country (https://www.worldometers.info/world-population/population-by-country/) relying on data extracted from Johns Hopkins University Coronavirus Resource Center.[2] https://coronavirus.jhu.edu/map.html
Data in the last column (mathematical estimates) come from the Imperial College report[5] issued on 30 March 2020. https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-Europe-estimates-and-NPI-impact-30-03-2020.pdf
To calculate the approximate incidence in each country, the 2020 population by country was found on the Worldometer webpage: https://www.worldometers.info/world-population/population-by-country/

COVID-19, as well as the specifics that cardiologists and cardiac surgeons must know in order to tackle prevention and treatment issues involving their patients exposed to SARS-CoV-2.

Current epidemiology

As of today, the pandemic has undergone three main phases in terms of geographical scope. From late December 2019 to mid-late February, the main focus was Asia, with China having the highest concentration of outbreaks, followed by South Korea. After applying severe containment measures, the dissemination has been controlled in these countries and the second phase, still ongoing, affected European countries from mid-February, Italy foremost followed by Spain. The third phase started in mid-March and is characterized by a pronounced increase in cases in the USA.[2–5]

Table 1 summarizes COVID-19 statistics in most affected European countries as of 4 May 2020.

As regards baseline epidemiological characteristics, in China COVID-19 affected mostly people aged 30–79 years (87%), whereas cases over 80 years and below 19 years were relatively rare (3% and 2%, respectively).[6] Mean age ranges from 47 to 56 years in the largest reports, men are more likely to present COVID-19 (~65% of cases), ~15% of cases occur in smokers, and 25–30% of patients present concomitant diseases, with up to 40% of these being cardiovascular diseases, of which remarkably hypertension makes up 15–30%.[7–9] A recent meta-analysis found that hypertension, cardio-cerebrovascular disease, and diabetes in patients with COVID-19 were present in 17.1, 16.4, and 9.7%, respectively.[10] Healthcare workers are a group at risk, with prevalence varying according to the setting, e.g. they represent 3.8% of infected individuals in China[6] and 15.5% in Spain.[11]

The virus and pathogenesis

Coronaviruses are found in a variety of birds and mammals throughout the world and have a proclivity for emergence. In the past 20 years, three novel human coronaviruses have emerged, first SARS-CoV in 2002, Middle East respiratory syndrome (MERS)-CoV in 2012, and the causative agent of COVID-19, SARS-CoV-2, in 2019, and all three are believed to have originated in bats.[12–14] SARS-CoV-2 is a beta-b coronavirus genetically related to but distinct from SARS-CoV.[15] To gain entry into the host cell, the SARS-CoV-2 S glycoprotein binds the cellular receptor angiotensin-converting enzyme 2 (ACE2), which is also the receptor for the original SARS-CoV.[13] *Figure 1* shows the life cycle of SARS-CoV-2.

SARS-CoV (basic reproduction number-R_0 1.8–2.5), MERS-CoV, and SARS-CoV-2 (R_0 2.4–3.8) are primarily transmitted by the respiratory route on large droplet nuclei, close contact with infected people, or fomites. The main form of SARS-CoV-2 transmission is person to person through respiratory droplets in the air (reaching up to 2 m) and landing on surfaces, which can transmit the virus even after several days.[16,17] SARS-CoV-2 is the most infectious of the three, with each case causing an estimated 2–4 new cases, whereas the R_0 of influenza virus varies according to the season from 1.2 to 2.[14] Pre-symptomatic and first symptomatic days correlate with a higher viral load, which has been proved to entail a higher risk of transmission.[18]

The virus targets cells lining the respiratory epithelium, causing a range of symptomology from asymptomatic infection to severe end-stage lung disease requiring mechanical ventilation as for ARDS.[14] Disease severity is likely to be a combination of direct virus-induced pathology and the host inflammatory response to infection. In brief, two mechanisms have been proposed for lung injury leading to ARDS during coronavirus infections in humans. First, ACE2 not only

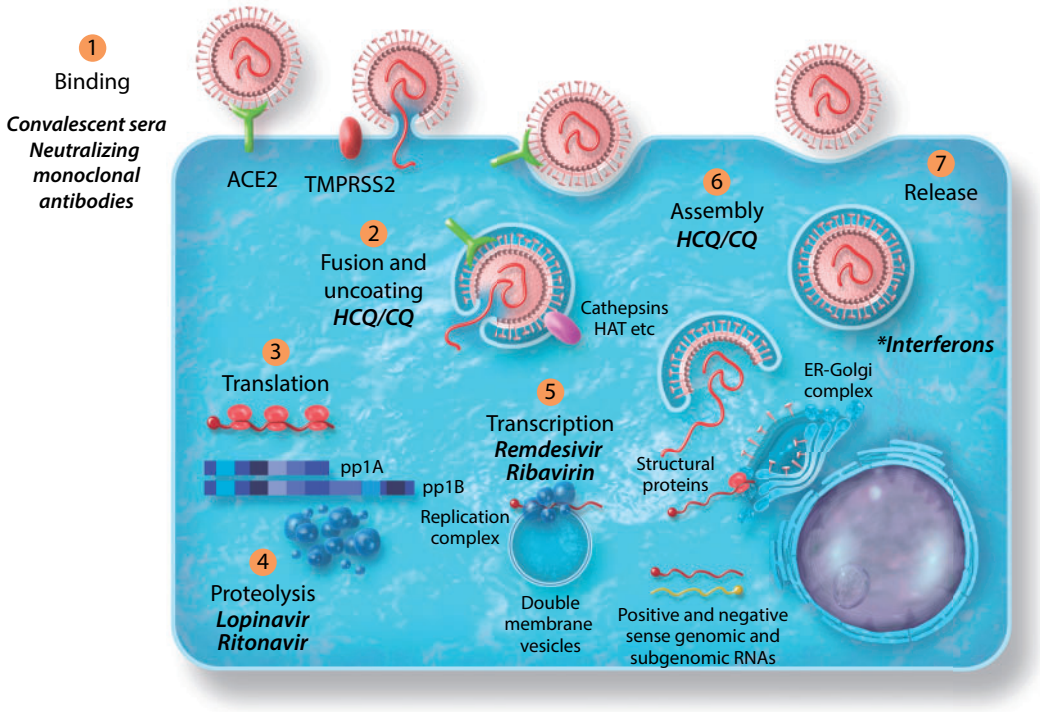

Figure 1 Life cycle of SARS-CoV-2 and potential medical countermeasures. The positive-sense RNA genome of SARS-CoV2 is encapsulated in a viral envelope studded with four viral structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). SARS-CoV-2 gains entry into the host cell via binding of the S protein to the cellular receptor angiotensin-converting enzyme 2 (ACE2). Spike glycoprotein rearrangement that primes fusion of viral and host membranes is driven by host proteases (TMPRSS2, cathepsins, HAT, furin, etc.), after which the genome is deposited into the cytoplasm and translation of ORF1a/b ensues. The polyproteins generated from ORF1a/b are cleaved by viral proteases liberating 16 non-structural proteins that guide virus replication. The replication complex is formed on double membrane vesicles, creating both genome-length RNA as well as subgenomic RNAs that encode structure genes S, E, M, and N as well as accessory ORFs that probably play roles in modulating the host response. New virus particles are assembled on membranes derived from the ER–Golgi complex and then transported out of the cell via the secretory pathway. Medical countermeasures are shown in italics adjacent to the viral function they are thought to attack. Convalescent sera and neutralizing monoclonal antibodies should inhibit virus binding to ACE2 and entry. Chloroquine is thought to interrupt entry and/or egress. Protease inhibitors such as lopinavir/ritonavir are thought to prevent polyprotein proteolysis. Nucleoside analogues such as remdesivir and ribavirin are thought to prevent viral RNA synthesis. *Interferons induce the expression of antiviral and immunomodulatory genes that could affect multiple aspects of the virus replication cycle HCQ/CQ, hydroxychloroquine/chloroquine.

acts as mediator of coronavirus entry into the cells, but also contributes to diffuse alveolar damage through imbalances in the renin–angiotensin system due to its down-regulation, activated by the S protein. Secondly, some coronavirus proteins are strong inducers of apoptosis of cell lines derived from different organs, primarily the lungs.[19]

Alveolar macrophages also play an important role, since their activation underlies the cytokine storm phenomenon: a massive release of macrophage migration inhibitory factor (MIF), tumour necrosis factor (TNF)-α, and interleukin (IL)-1, IL-2R, IL-6, IL-8, and IL-10, attracting neutrophils that will release leukotrienes, oxidants, and proteases, which will lead to the typical ARDS pathology with acute diffuse alveolar damage, pulmonary oedema, and formation of hyaline membranes.

In summary, there are two phases in SARS-CoV-2 infection: during early infection (up to 7–10 days), viral syndrome predominates with a high viral load in the upper and lower respiratory tract; in a second phase, viral pneumonia can develop; and finally the viral infection can trigger the host inflammatory and procoagulant responses with SIRS, ARDS, shock, and cardiac failure (see *Figure 2*).

Pro-inflammatory and pro-coagulant states as triggers of cardiovascular events

ACE2 receptors are also located in the heart, kidney, brain, and gut, and therefore COVID-19 might cause a plethora of extrapulmonary manifestations, including cardiovascular ones.[20] In the case of heart injury, preliminary data indicate that pericytes with high expression of ACE2 might act as the target cardiac cell of SARS-CoV-2 and, once damaged, capillary endothelial cell dysfunction arises, inducing microvascular dysfunction.[21,22] In addition to the immune pathway, leading to increased endothelial dysfunction, itself leading to ischaemic or

arrhythmic events as a consequence of a pro-inflammatory cascade, SARS-CoV-2 induces coagulation disorders that might also decompensate pre-existing cardiovascular diseases.[23] In brief, systemic hyperinflammatory response, coagulation disorders involving prothrombotic states, microvascular injury, stress cardiomyopathy, myocardial injury secondary to oxygen supply–demand mismatch, and acute coronary syndromes triggered by plaque instability are major pathways for cardiovascular events in COVID-19 patients.[21–30] Moreover, social distancing and social isolation as preventive measures also seem to increase cardiovascular risk.[22]

Clinical manifestations

The most common symptoms of COVID-19 are fever and dry cough, together with shortness of breath (*Table 2*). More recently, anosmia, hyposmia, and dysgeusia have also been described as largely characteristic during the initial phase of COVID-19.[31] Meanwhile, digestive symptoms can also be found. Common blood test parameters include lymphocytopenia, increased IL-6, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, ferritin, transaminases, high-sensitivity troponin, and N-terminal pro-brain natriuretic peptide (NT-pro-BNP). Meanwhile, procalcitonin levels are usually very low, which helps to differentiate COVID-19 from acute bacterial infection. It should be noted that these parameters evolve dynamically throughout the course of the disease: for instance, white blood cell count often progresses from normal total counts with lymphocytopenia to leukopenia in severe cases. Moreover, the neutrophil–lymphocyte ratio appears to be associated with illness severity.[32]

Radiological manifestations range from normal chest X-ray or CT scan in ~10% of cases to lung fibrosis.[33] More commonly, COVID-19 presents as pneumonia (bilateral in around half of the cases) with reticular nodular or ground-glass opacities.

Approximately 5–10% of patients require admission to the intensive care unit (ICU) and mechanical ventilation.[34] Among patients with pneumonia, ICU admission is required in 23–26% of cases and ARDS develops in 16–42% of them.[8,9,14,35] Shock has been described in up to 20% of cases,[9] but most series range between 1% and 8%.

Figure 2 shows the different stages within COVID-19 natural history and their correlation with pathophysiology. Onset of pulmonary symptoms occurs at the transition from a viral phase characterized by high viral load and relatively low inflammation to a host inflammatory response phase characterized by increasing inflammation and coagulation disorders. Typically, complications appear around days 10–12 after initial symptoms, often related to the triggering of an inflammatory cascade leading to the 'cytokine storm'.[36]

Cardiovascular manifestations

Table 3 shows a summary of the cardiovascular manifestations and complications related to COVID-19, as well as the guidance launched by scientific societies for their prevention and management. Although empirical data are lacking and the prevalence of cardiovascular events during and after COVID-19 has still not been described yet, it appears that cardiovascular events, especially myocarditis, are relatively common.[37–44]

Meanwhile, the COVID-19 pandemic seems to be associated with a decrease in consultations pertaining to cardiovascular events in non-COVID-19 patients. Studies from the USA, Italy, and Spain showed approximate reductions of 40% in ST-segment elevation myocardial infarction (STEMI) activations in cardiac catheterization laboratories and significant reductions in hospitalization rates due to acute coronary syndromes.[45–47] The Italian report also described a concomitant increase in mortality rates compared with the previous year, which was not fully explained by COVID-19-related mortality, therefore raising the question of whether some patients might have died of acute coronary syndromes without seeking medical attention. Regarding cardiac arrest, data from Lombardy in Italy showed an increase of out-of-hospital cardiac arrest incidence strongly associated with the cumulative incidence of COVID-19.[48] A study from Wuhan in China showed that survival of patients with COVID-19 suffering in-hospital cardiac arrest was extremely low at 30 days (2.9%).[49]

Finally, it should be borne in mind that acute pulmonary injury can potentially resemble pulmonary oedema, and thus differential diagnosis in patients with a prior history of heart failure is key, given the associated therapeutic implications [e.g. bilevel positive airway pressure (BiPAP) is to be avoided in COVID-19 patients]. The same is applicable to COVID-19 patients presenting with chest pain and elevated levels of troponin and to differentiating it from myocarditis.

Diagnosis

Laboratory diagnosis is a priority for clinical management and outbreak control of COVID-19. Respiratory samples have the greatest yield, but other specimens such as blood and stools can also be used; however, evidence on their efficacy is lacking.[50,51] Real-time reverse-transcription polymerase chain reaction is the current gold standard.[50] Detection of total antibodies, IgM and IgG, against SARS-CoV-2 in blood samples, may be non-sensitive during the first 7–14 days of disease.[52] Performing combined testing strategies with PCR and antibodies increases sensitivity to 90%.[51]

Clinicians should consider testing for other respiratory pathogens using routine laboratory procedures if individual case management requires because both viral and bacterial co-infections can occur.[53] Yet, in the context of epidemics, patients with a clinical presentation and radiological pattern that is compatible are assumed to have COVID-19, despite a negative (or unavailable) molecular or viral antigen detection test. However, clinical diagnosis should also take account of the clinical manifestations described in most series being constrained by a major population selection bias, with severe patients being more likely to be included in the studies.

Prognosis focused on cardiovascular risk factors

Older age is the most widely recognized epidemiological risk factor of mortality (*Table 4*). Mortality below 50 years is uncommon, but thereafter it doubles in each decade of life, going from 2% in the 50s to 16% or more in the 80s. Among comorbidities, hypertension and diabetes are also found among patients presenting poor outcomes, yet it should be noted that these both could be correlated to advanced age. Li *et al.* found that the percentage of patients with hypertension, cerebrovascular diseases, and diabetes

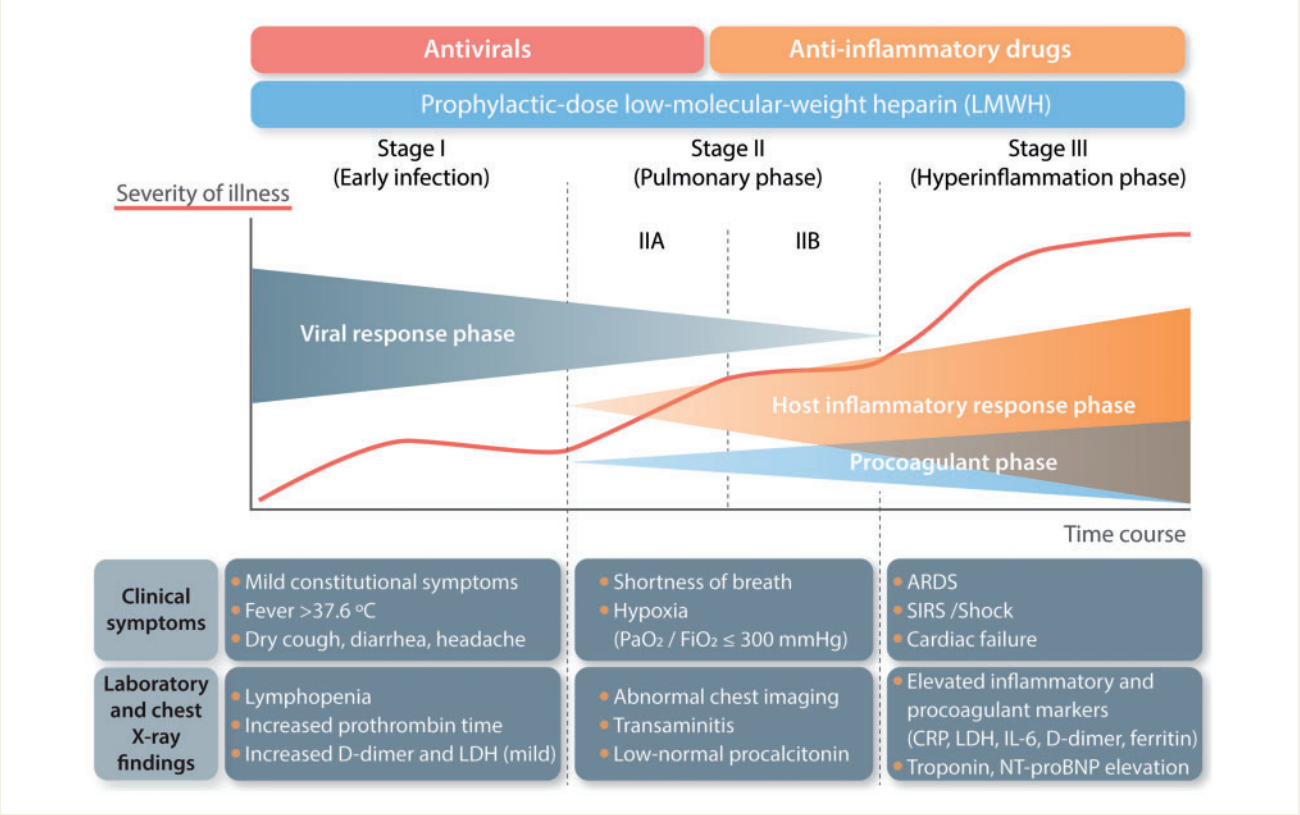

Figure 2 Clinical stages of COVID-19 (adapted with permission from Siddiqu and Mehra[125]). During the first days from disease onset, patients typically present a first phase with symptoms resembling an upper respiratory tract viral infection, mostly characterized by fever and coughing. Over days 8–12 there is a transition to an inflammatory phase during which pulmonary symptoms such as shortness of breath might appear. In those patients progressing to the hyperinflammatory phase with relevant lung involvement, the risk of ARDS is notable. In addition, during this late phase, patients are at higher risk of suffering thrombotic and embolic events due to a procoagulant state. ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; IL-1, interleukin 1; IL-6, interleukin 6; LDH, lactate dehydrogenase; NT-pro-BNP, natriuretic pro-brain natriuretic peptide; SIRS, systemic inflammatory response syndrome.

was two-fold, three-fold, and two-fold higher, repspectively in patients admitted to the ICU than in patients not presenting severe or critical COVID-19, and that acute cardiac injury was also ~13-fold higher in the former group of patients.[10] Shi *et al.* also found a 10-fold higher mortality among patients presenting with cardiac injury in a cohort of 416 patients with COVID-19, and predictors of cardiac injury included epidemiological (older age, comorbidities), analytical (leukocytosis, CRP, procalcitonin, creatine kinase, myohaemoglobin, high-sensitivity troponin I, NT-pro-BNP, aspartate aminotansferase (AST), and creatinine], and higher radiological (multiple mottling and ground-glass opacities).[54] Other studies have found that high levels of D-dimer, NT-pro-BNP, and high-sensitivity troponin I are strongly associated with acute cardiac injury and poor prognosis.[38] More recently, Argulian and colleagues found that right ventricular dilation in the echocardiography is associated with an increased risk of in-hospital death in a large series of patients hospitalized with COVID-19.[55]

High fever and dyspnoea on admission, and developing respiratory insufficiency have been commonly linked to poorer outcomes, as have high levels of D-dimer, LDH, IL-6, and transaminases, and low total lymphocyte count and CD3 and CD4 T-cell counts. Bilateral lung involvement as opposed to unilateral involvement does not seem to be associated with poorer mortality in most studies, yet Zhang *et al.* found that multilobar involvement was significantly associated with the severe/critical COVID-19 subtype.[56]

COVID-19 treatment and cardiovascular drugs

Currently there are no approved therapies specific to human coronavirus, and multiple medical countermeasures including direct acting antivirals (DAAs), host-targeted antivirals, and immunomodulators are being prescribed off-label for treating COVID-19 based on past observational studies for other coronaviruses as an attempt to diminish disease severity.[57] In addition, multiple therapies are currently being evaluated in randomized control trials to conclusively determine efficacy,[58,59] with >300 registered trials ongoing related to COVID-19.[60]

Table 5 shows a summary of the drugs utilized and proposed for treating COVID-19 to date.

Table 2 Summary of clinical and imaging manifestations of COVID-19

Study	Country	Sample size	Signs and symptoms, median incubation period (MIC)	Radiological findings	Complications
Wu and McGoogan[6]	China	72 314 (62% confirmed)	1% asymptomatic Definitions according to severity of presentation: mild, non-pneumonia and mild pneumonia; severe, dyspnoea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24–48 h; critical, respiratory failure, septic shock, and/or multiple organ dysfunction or failure	–	Mild 81%, severe 14%, critical 5% Deaths 2.3% (49% among critically ill)
Guan *et al.*[7]	China	1099	MIC 4 days (IQR 2–7) Fever (43.8% on admission and 88.7% during hospitalization); cough 67.8% Lymphocytopenia 83.2% Diarrhoea, 3.8%	Ground-glass opacity, 56.4% Normal CT, 14.7% (17.9% in patients with non-severe disease and 2.4% in patients with severe disease)	ICU: 5% IMV: 2.3% Death: 1.4%
Zhang *et al.*[56]	China	645	Patients with pneumonia presented higher rates of fever, cough, expectoration, and headache, lower lymphocytes, albumin, serum sodium levels, and higher total bilirubin, creatine kinase, lactate dehydrogenase, and C-reactive protein levels, and lower oxygenation index	Presence of either ground-glass opacities or consolidation, or both 88.8% Bilateral lung disease 67% Number of lobes affected: 1, 21.5%; 2, 31.6%; 3, 136, 21.1%; 4, 10.2%; 5, 4.4%	ICU: 0.6% ARDS: 2.2% IMV: 1.4% Shock: 0.3% ECMO: 0% Death: 0%
Zhou *et al.*[13]	China	191	MIC 11 days (8–14)Fever 94%, cough 79%, sputum 23%, fatigue 23%, myalgia 15%, diarrhoea 5%, nausea, and vomiting 4%.Elevated LDH 67%, lymphocytopenia 40%, elevated ferritin 80%, elevated D-dimer 42%, elevated ALT 31%.	Consolidation 59% Ground-glass opacity 71% Bilateral pulmonary infiltration 75%	ICU: 26% ARDS: 31% IMV: 17% ECMO: 2% Shock: 20% Acute cardiac injury: 17% LOS: 11 days (IQR 7–14) Death: 28.3%
Wu *et al.*[35]	China	201 (all with pneumonia)	Fever 93.5%, cough 81.1%, dyspnoea 39.8%, and fatigue or myalgia 32.3%	Bilateral infiltrates 95%, unilateral infiltrates 5%	ICU: 26.4% ARDS: 41.8% Death: 21.9%

Continued

Table 2 *Continued*

Study	Country	Sample size	Signs and symptoms, median incubation period (MIC)	Radiological findings	Complications
Wang *et al.*[14]	China	138	MIC 5 days (to dyspnoea; 7 days to admission) Fever 98.6%, fatigue 69.6%, dry cough 59.4%. Lymphocytopenia 70.3%, prolonged prothrombin time 58%, elevated LDH 39.9%	Bilateral patchy shadows or ground-glass opacity in all patients	ICU: 26.1% ARDS: 15.9% IMV: 12.3% Arrhythmia: 11.6% Shock: 8% Death: 4.3%
Chen *et al.*[8]	China	99 (all with pneumonia)	Fever 83%, cough (82%, shortness of breath 31%, muscle ache 11%, confusion 9%, headache 8%, sore throat 5%, rhinorrhoea 4%, chest pain 2%, diarrhoea 2%, nausea and vomiting 1%.	Bilateral pneumonia 75%, unilateral pneumonia 25%, multiple mottling and ground-glass opacity 14%, pneumothorax 1%.	ICU: 23% ARDS: 17% IMV: 4% ECMO: 3% Shock: 4% Death: 11%
Spiteri *et al.*[94]	WHO European region	38	Asymptomatic 6.4% Fever 64.5%, cough 45.2%, fatigue 25.8%, headache 19.3%, sore throat 6.4%, rhinorrhoea 6.4%, shortness of breath 6.4%	Pneumonia 11.8%	ICU: 8.8% Death: 2.9%
Korea Centers for Disease Control and Prevention[95]	Korea	28	MIC 4.1 days Asymptomatic 10.7% Fever 32.1%, sore throat 32.1%, cough or sputum 17.9%, chills 17.9%, muscle ache 14.3%	Pneumonia 64.3%	LOS: 12.7 days (8–19)
Arentz *et al.*[96]	USA	21 (all in ICU)	Shortness of breath 76.2%, fever 52.4%, cough 47.6%	Bilateral reticular nodular opacities 52.4%, ground-glass opacities 47.6%, pleural effusion 28.6%, focal consolidation 19%, pulmonary oedema 9.5%, venous congestion 4.8%, atelectasis 4.8%, normal 4.8%.	ICU: 100% ARDS: 95.2% IMV: 71% Cardiac injury: 33% Death: 67%

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMV, invasive mechanical ventilation; LDH, lactate dehydrogenase; LOS, length of stay.

Table 3 Cardiovascular manifestations in COVID-19

Study	Type of study	Country	Main findings
Original studies and case reports			
Shi *et al.*[54]	Prospective cohort	China	82/416 (19.7%) patients presented cardiac injury.
Deng *et al.*[37]	Retrospective study of 112 patients with COVID-19	China	14 (12.5%) presented abnormalities similar to myocarditis, but without typical signs on echocardiography and electrocardiogram.
Gao *et al.*[38]	Retrospective, observational registry of 102 patients with severe COVID-19, only 54 of whom entered the analysis (NCT04292964)	China	Patients with high NT-pro-BNP values (>88.64 pg/mL) had a significantly increased risk of death during follow-up
Bangalore *et al.*[39]	Cases series of 18 patients	USA	18 patients with COVID-19 presenting with ST-segment elevation, 10 of whom had non-coronary myocardial injury
Sala *et al.*[40]	Case report	Italy	Acute myocarditis presenting as a reverse Tako-Tsubo syndrome
Dong *et al.*[41]	Series of four cases	China	Four patients with prior cardiovascular (CV) disease developed end-stage heart failure during COVID-19 (2 of them died).
Zeng *et al.*[42]	Case report	China	Fulminant myocarditis
Kim *et al.*[43]	Case report	China	Myocarditis in a 21-year-old patient
Zhang *et al.*[44]	Series of three cases	China	Coagulopathy and antiphospholipid antibodies
Reviews and perspectives			
Xiong *et al.*[24]	Narrative review	China, UK	Coronaviruses, including SARS and MERS, have short- and long-term implications for the CV system. Patients presenting with CV manifestations seem to more frequently require ICU admission.
Madjid *et al.*[25]	Narrative review	USA	Acute cardiac injury determined by elevated high-sensitivity troponin levels is commonly observed in severe cases and is strongly associated with mortality
Driggin *et al.*[26]	Narrative review	USA	Patients with CV comorbidities more frequently require ICU admission. COVID-19 can lead to exacerbation of previous CV disease or to specific complications such as myocardial injury, myocarditis, and acute coronary syndromes, cardiogenic shock, or arrhythmia.
Liu *et al.*[27]	Narrative review	USA	The CV system is commonly involved in early phases of COVID-19. Microangiopathy and thrombosis seem to be the main mechanisms of cardiac injury. Levels of hsTrP and NPs are prognostic.
Kochi *et al.*[28]	Narrative review	Italy and Switzerland	Close monitoring of potential arrhythmogenic effects of both COVID-19 itself and antiviral medication is advisable, especially in patients with previous CV disease.
Libby[29]	Short review and perspective	USA	There are likely to be multiple pathophysiological pathways involved in cardiac injury during COVID-19, which call for precaution in deciding therapeutic approaches until more robust evidence is available
Guidance			
Edelson *et al.*[97]	Guidelines	USA	Interim guidance for basic and advanced life support

Continued

Table 3 *Continued*

Study	Type of study	Country	Main findings
Han *et al.*[89]	Experts consensus	China	Clinical management of patients with severe emergent CV diseases
Welt *et al.*[90]	Consensus statement	USA	Catheterization laboratory considerations
Romaguera *et al.*[88]	Consensus statement	Spain	Considerations on the invasive management of ischaemic and structural heart disease during the COVID-19 coronavirus outbreak
Hunt *et al.*[98]	Living guidance (updated weekly)	UK	Prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19
Zhai *et al.*[99]	Consensus statement	China	Prevention and treatment of venous thromboembolism associated to COVID-19
Zhai *et al.*[88]	Consensus statement	China	Prevention and treatment of venous thromboembolism
Wood *et al.*[93]	Summary of guidance from professional societies (North American Society Leadership)	USA	Safe reintroduction of cardiovascular services
European Society of Cardiology	Special section on website	Europe	https://www.escardio.org/Education/COVID-19-and-Cardiology
American Heart Association	Special section on website	USA	https://www.heart.org/en/coronavirus
American College of Cardiology	COVID-19 hub on website	USA	https://www.acc.org/latest-in-cardiology/features/accs-coronavirus-disease-2019-covid-19-hub

The drugs currently under exploration are thought to target various aspects of the virus life cycle (*Figure 1*). The objectives of treatment are three-fold (*Figure 2*): first, to administer an early antiviral treatment that will be more effective on the first 7–14 days of infection, which is when the viral load is highest in the upper and lower respiratory tract; secondly, to address the cytokine storm in order to prevent onset of ARDS and avoid the need for mechanical ventilation, which has a mortality of ∼50%; and, thirdly, to reduce the likelihood of major thrombo-embolic events.

Case study 2: A 43-year-old male with a history of non-compaction cardiomyopathy bearing an implantable cardioverter defibrillator for primary prevention of sudden cardiac death underwent cardiac transplantation on 3 March. During the post-operative period, the patient shared nursing staff with a patient who several days later tested positive for SARS-CoV-2. On 16 March, he tested positive for SARS-CoV-2, developing a moderate COVID-19 pneumonia. The contact tracing revealed 10 exposures but no secondary cases. Corticosteroids were maintained at 0.5 mg/kg and tacrolimus was stopped during the 10-day lopinavir/ritonavir therapy. Tacrolimus serum levels evolved from 20 to 15 ng/mL during the 10-day period off the drug (the patient also received hydroxychloroquine and azithromycin without significant QT prolongation). He evolved well in a general ward and was discharged.

Takeaway: Nosocomial SARS-CoV-2 infection is possible and some antiviral SARS-CoV-2 therapies have significant pharmacokinetic and pharmacodynamic (QT prolongation) interactions.

Hydroxychloroquine alone or combined with azithromycin, lopinavir/ritonavir, and remdesivir has been the most used off-label antiviral drugs. Hydroxychloroquine and chloroquine alone or combined with azithromycin may increase in hospital mortality and the risk of ventricular arrhythmia due to QT prolongation,[61,62] and their use is currently not recommended outside of clinical trials.[63] Lopinavir/ritonavir may also increase the QTc interval, has significant drug–drug interactions (as shown in case study 2) and side effects, and a randomized clinical trial did not show efficacy.[64] Performance of an ECG is mandatory and periodic ECG monitoring should be considered in patients taking these drugs. Remdesivir was recently approved (1 May) by the US FDA for an emergency use authorization for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease.[65–67] The Liverpool web page periodically updates drug interactions with COVID-19 medications (www.covid19-druginteractions.org).[68]

Routine use of systemic corticosteroids is not recommended for preventing or treating ARDS in COVID-19 patients unless they are indicated for other reasons.[69,70] Preliminary studies with IL-6 inhibitors (e.g. tocilizumab, see *Table 5*) have shown efficacy in patients with severe or critical COVID-19.[71,72] The use of corticosteroids or other anti-inflammatories is recommended in the context of clinical trials. Due to the procoagulant state caused by SARS-CoV-2, subcutaneous low molecular weight heparin prophylaxis is recommended for all hospitalized patients if there is no contraindication.[73] Weight-adjusted intermediate doses of heparin are recommended in patients with risk factors for venous thrombo-embolism, and patients with thrombo-embolic disease must be fully anticoagulated.[73]

Given the initial evidence pointing to a higher mortality in patients with hypertension,[9,35] there has been a discussion, mainly generated

Table 4 Summary of studies assessing prognostic factors of mortality and complications in COVID-19

Study	Sample size	Endpoint/s	Risk factors	Protective factors
Zhou *et al.*[13]	191	In-hospital death	Older age, higher SOFA score, and high D-dimer greater on admission	–
Wang *et al.*[14]	138	ICU admission	Older age, comorbidities, dyspnoea	–
Yang *et al.*[100]	52, all admitted to ICU	In-hospital death	Older age, ARDS, mechanical ventilation	–
Zhang *et al.*[56]	645	Severe/critical COVID-19 categories	Myalgia, dyspnoea, nausea and vomiting, lymphocytopenia, higher creatinine and number of lobes radiologically involved at admission	–
Shi *et al.*[54]	416	Cardiac injury (associated with higher in-hospital death)	Older age, more comorbidities, higher leucocyte counts, higher levels of C-reactive protein, procalcitonin, CK-MB, myohaemoglobin, high-sensitivity troponin I, NT-pro-BNP, AST, and creatinine, and higher proportion of multiple mottling and ground-glass opacity	–
Wu *et al.*[35]	201	ARDS and progression to death in patients with ARDS	ARDS: older age, high fever, comorbidities, neutrophilia, lymphocytopenia (as well as lower CD3 and CD4 T-cell counts), elevated end-organ-related indices (e.g. AST, urea, LDH), elevated inflammation-related indices (high-sensitivity C-reactive protein and serum ferritin), and elevated coagulation function-related indicators (prothrombin time and D-dimer).Death in ARDS: older age, lower proportion of high fever, hypertension, neutrophilia, elevated bilirubin, urea, LDH, D-dimer, cystatin C, and IL-6.	Death in ARDS: high fever, treatment with methylprednisolone and antivirals.
Huang *et al.*[101]	41	ICU admission	Dyspnoea, neutrophilia, lymphocytopenia, enlarged prothrombin time, elevated D-dimer, transaminases, bilirubin, troponin I, IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNFα, and lower albumin	High fever
Liu *et al.*[102]	78	Clinical deterioration, and likeliness of high-level respiratory support	Older age, history of smoking, high fever, respiratory failure, low albumin, high C-reactive protein	–
Sun *et al.*[103]	600	Progression to critical condition	Older age, lymphocytopenia, oxygen supplementation and multiple/extensive pulmonary radiographic infiltrations	–
Mo *et al.*[104]	155	Refractory pneumonia*	Male sex, anorexia, and high fever at admission, receiving oxygen, expectorants, corticosteroids, lopinavir/ritonavir, immune enhancer (thymalfasin, immunoglobulins)	–
Wang *et al.*[105]	68	SpO_2 <90% (related to death)	Older age, comorbidities, elevated IL-6, IL-10, LDH, and C-reactive protein	–

*Defined as those cases not fulfilling all the following: (i) obvious alleviation of respiratory symptoms (e.g. cough, chest distress. and shortness of breath) after treatment; (ii) maintenance of normal body temperature for ≥3 days without the use of corticosteroids or antipyretics; (iii) improvement in radiological abnormalities on chest CT or X-ray after treatment; and (iv) a hospital stay of ≤10 days.

through the media, regarding the necessity of avoiding the use of ACE inhibitors and angiotensin receptor blockers (ARBs) to increase the risk of infection and the severity of COVID-19. However, available evidence indicates that neither likelihood of contracting COVID-19 nor mortality is increased in patients receiving those drugs.[74–77] On 13 March, the Council on Hypertension of the European Society of Cardiology launched a statement strongly recommending that physicians and patients should continue treatment with their usual antihypertensive therapy.[78] More recently, a special Task Force within the European Society of Hypertension critically

Table 5 Overview of drugs used for COVID-19 treatment

Drug name	Drug family/mechanism of action	Recommended doses and length of therapy in adults	Potential secondary effects	Main potential interactions with cardiovascular drugs	References
Chloroquine/ hydroxychloroquine*	Antimalarial; unknown mechanism	Loading dose 400 mg p.o. b.i.d. first day followed by 200 mg b.i.d. (5–14 days)	Ocular disturbances, reversible after early discontinuation; anorexia, weight loss, nausea, diarrhoea; elevation of liver enzymes; hypoglycaemia; hearing loss. QTc prolongation.	Amiodarone, flecainide, and other anti-arrhytmics; direct inhibitors of factor Xa; potential mild interaction with some beta-blockers (propranolol, nebivolol, metoprolol, timolol) and verapamil.	106–111 A recent statement by the International Society of Antimicrobial Chemotherapy[111] expressed concern regarding the inclusion criteria of the study of Gautret *et al.*[110]
Azithromycin (combined with hydroxychloroquine)	Macrolyde; unknown mechanism	Loading dose 500 mg p.o. the first day followed by 250 mg p.o. 4 days (5 days)	Diarrhoea, loose stools, nausea, abdominal pain, vomiting; QTc prolongation.	Digoxin, coumarins	110
Lopinavir/ritonavir	HIV protease inhibitors	400/100 mg p.o. b.i.d. Individualized duration (maximum 14 days)	Frequent: diarrhoea, nausea, vomiting, altered lipid profile; uncommon: pancreatitis, QTc prolongation	Potent P450 inhibitor. Anti-arrhythmics, antiplatelet, anticoagulants, and other (some statins, eplerenone, aliskiren, ivabradine, sildenafil, calcium channel blockers, beta-blockers, digoxin, doxazosin, dinitrate isosorbide, etc.)	64,112,113
Remdesivir	Non-nucleoside analogue. Interferes with viral RNA polymerization.	Loading dose 200 mg i.v. the first day and 100 mg/day from day 2 to 10	Hypotension during infusion; gastrointestinal (nausea, vomiting, diarrhoea, constipation, abdominal pain)	Carbamazepine, phenobarbital, rifampin and other P450 inducers can decrease remdesivir levels. Caution in concomitant use with vasopressors and inotropes due to the added haemodynamic effects.	113–116 Recent FDA approval[65] based on interim analyses of the NIH-sponsored ACTT trial[66] and the SIMPLE trial (Gilead)[67]
Tocilizumab†	IL-6 inhibitor	≥80 kg body weight: two doses of 600 mg i.v. separated 12 h of from each other<80 kg body weight: 600 mg i.v. followed by 400 mg i.v. 12 h laterExceptionally, a third dose could be administered 16–24 h later	Upper respiratory tract infections, rhinopharyngitis, headache, hypertension, and elevation of transaminases	Potential mild interactions with amiodarone, quinidine, some anticoagulants, and antiplatelets	71,72,117
Sarilumab	IL-6 inhibitor	Single dose of 200–400 mg i.v.	Neutropenia, elevated transaminases, point of injection	Similar to tocilizumab	118

Continued

Table 5 *Continued*

Drug name	Drug family/mechanism of action	Recommended doses and length of therapy in adults	Potential secondary effects	Main potential interactions with cardiovascular drugs	References
			erythema, upper respiratory tract and urinary infections		
β-Interferon 1B	Immune modulator	250 mg s.c. every 48 h for 14 days	Fever, headache, myastenia, rash, nausea, diarrhoea, lymphocytopenia, weakness, flu-like syndrome	Theophylline and oral anticoagulants	113,117,118 NCT02845843 (in combination with lopinavir/ritonavir)
α-Interferon 2B	Immune modulator	5 million units, inhaled, b.i.d. for 5–7 days	Similar to β-IFN	Theophylline and oral anticoagulants	117,118 ChiCTR2000029308
Ribavirin (in combination with IFN-α or lopinavir/ritonavir)	Synthetic nucleoside antiviral	500 mg i.v. b.i.d. or t.i.d.; up to 10 days	Gastrointestinal, mood disorders, skin rash, severe anaemia	Digoxin, dicumarinics	117,118
Other drugs and interventions under evaluation (not enough evidence for their recommendation)					
Colchicine	Anti-inflammatory activity	0.5 mg b.i.d.	Nausea, diarrhoea, myalgia, tachycardia	Statins, diltiazem, aspirin	118 NCT04322682, NCT04326790, NCT04322565
Convalescent patient serum	IgG binding antibodies against SARS-CoV-2 from donors recovered from COVID-19	Administered in five patients 10–22 days after admission			119,120 Used in patients with ARDS
Angiotensin receptor blockers (e.g. losartan)	Up-regulation of ACE2 receptor				81 NCT04312009 and NCT04311177
Dipyridamole	Suppresses SARS-CoV-2 replication *in vitro*				121
Amiodarone	Alters endosomes and inhibits SARS coronavirus infection at a post-endosomal level.				122,123
Statins	Up-regulation of ACE2 receptor				81 Potentially useful to decrease ARDS severity
Siluximab	IL-6 inhibitor				118 SISCO study (Italy)
Eculizumab	Complement inhibitor				118 Potentially useful to avoid ARDS

Continued

Table 5 *Continued*

Drug name	Drug family/mechanism of action	Recommended doses and length of therapy in adults	Potential secondary effects	Main potential interactions with cardiovascular drugs	References
					by disrupting inflammatory cascade through C5 inhibition [117]
Danoprevir/ritonavir	Hepatitis C virus protease inhibitor				Three patients cured in Ninth Hospital of Nanchang, China (unpublished data)
Favipiravir	Viral polymerase inhibitor				[124] Used for treating flu and Ebola. Data available for COVID-19 from a small open label trial [118]
Darunavir/cobicistat	HIV protease inhibitor + pharmacokinetic booster				Trial ongoing in China (NCT04252274) [118]
Arbidol (umifenovir)	Viral membrane fusion inhibitor				Several trials ongoing in China [118]
APN01	Human recombinant ACE2 analogue				Potential role on avoiding and treating ARDS NCT04287686 [118]
Leronlimab	Monoclonal antibody; inhibits HIV CCR5 receptors and reduces cytokine storm				[118]
Camrelizumab and timosine	Blocking antibodies				ChiCTR2000029806 and NCT04268537 [118]
Regeneron (REGN3048 and REGN 3051)	Combination of two monoclonal antibodies against the surface spike protein of SARS-CoV2				

*Proposed as a prophylactic agent for contacts.
†Indicated in patients presenting one or more of the following criteria: (i) interstitial pneumonia with severe respiratory failure; (ii) rapid respiratory worsening that requires mechanical ventilation (either invasive or non-invasive); (iii) non-respiratory organ failure (septic shock or SOFA score >3); and (iv) severe systemic inflammatory systemic response: IL-6 >40 pg/mL and/or D-dimer >1500 mg/dL.

reviewed the available evidence and came to the conclusion that it does not support a deleterious effect of renin–angiotensin blockers in COVID-19, observing increased lower respiratory tract infections and lung injury.[79] Moreover, Zhang *et al.* recently reported a significantly lower mortality rate among patients with hypertension receiving ACE inhibitors or ARBs during admission compared with other patients with hypertension hospitalized due to COVID-19.[80] Based on the knowledge of SARS-CoV-2 pathogenicity traits, some authors advocate conducting studies to test the efficacy of both ARBs and statins to treat severe COVID-19, arguing that up-regulated ACE2 receptor activity is associated with a reduced severity of ARDS.[81] There are currently two trials including patients without hypertension that are testing losartan (NCT04312009 and NCT04311177).[60]

Finally, there are some important points to be made for cardiovascular specialists regarding the management of critically ill patients in the context of COVID-19. First, due to general hospital overload and relative lack of ventilators, the avoidance of intubation in non-COVID-19 patients becomes even more relevant than usual. Secondly, differentiating patients with acute lung injury due to COVID-19 from patients with acute pulmonary oedema due to heart failure is crucial, since BiPAP should be avoided in the former. Thirdly, high-flow nasal cannula oxygen should be used in an effort to minimize alveolar injury prior to proceeding with intubation. Finally, where oro-tracheal intubation and mechanical ventilation are required, protective ventilation with relatively high pressures at the end of the expiratory period and low volumes is recommended.[34,69]

Prevention adapted to Cardiology and Cardiovascular Surgery

Once a first imported case of COVID-19 is confirmed and isolated, the potential for further exponential disease spread within the hospital and region is possible. Containment measures by tracking of contacts and quarantine are necessary to mitigate the risk of losing track of potentially infected individuals.[82] Increasing prevention practices in the hospital needs to be supported to a scale that initially may seem draconian to employees and healthcare providers. The risk of internal disease spread puts not only patients at risk, but also co-workers and their families, and ultimately the whole of society.

Facemasks should be used by all infected patients to avoid transmission. Therefore, isolation of suspected or confirmed contagious individuals is mandatory in any instance within the hospital with the physical ability to avoid propagation of the virus. Healthcare personnel need to adopt appropriate protective measures and avoid cross-contamination to other patients or co-workers. In this regard, preventive measures may continue to escalate within the hospital, for example to conventional surgical masks for non-suspicious personnel and patients, cancellation of face-to-face meetings, and so on.[82] Furthermore, surfaces (fomites) must be disinfected, and therefore frequent hand washing with soap and water is mandatory.

Full personal protection equipment (PPE) should be used following established protocols after appropriate training. PPE for healthcare professionals involved in the direct care of COVID-19 patients include the following elements: FFP3 respirators (filtering at least 99% of airborne particles)—FFP2 and N95 respirators (filtering 94% and 95% of particles, respectively) can be used if FFP3 are not available—fluid-resistant surgical masks (type IIR) provide barrier protection against droplets; goggles, full face shield, or visor, or polycarbonate safety spectacles for eye and face protection; gowns should be long sleeved and disposable; gloves; and fluid repellent.[82,83]

In addition to droplet and contact precautions, allocating COVID-19 (confirmed or suspected) patients in ICU cubicles with negative pressure to avoid propagation of the virus through aerosols that could reach outside the room and spread into clear areas should be pursued. In general terms, careful patient screening during urgent/emergent procedures is required, and adoption of full protection by means of meticulous donning and doffing of PPE needs to be considered along with staffing modifications. Also rescheduling of all non-urgent, elective procedures seems justified in order to avoid environmental and provider contamination. This underlines the need to develop individualized contingency plans, adapted to each cardiovascular team, and in a forward-looking way, i.e. with both the active epidemic phase and the progressive resumption of clinical and surgical activities in mind. These plans should be continuously updated. Managerial decisions and team coordination should rely on an increased use of virtual communication as opposed to face-to-face meetings. To prevent new infections involving either patients or staff, tailored triage systems largely based on telemedicine for programmed patients are of upmost importance, along with the set up of clean and dirty zones.[84,85] The latter should have all the appropriate protection measures. Patients should be allocated to the latter areas where there is evidence for the reasonable suspicion of infection or contact with infected individuals. It is advisable to perform all urgent procedures in specially equipped areas on the assumption that patients are infected.

When a new case is detected within the hospital, contact tracing includes other patients, staff, and close contacts before admission in cases where there is suspicion of community acquisition rather than nosocomial. The preventive medicine service and infection control units carry out surveys to identify contacts and perform tests on them. High-risk contacts among healthcare personnel imply pre-emptive isolation. *Figure 3* (Summarizing Illustration) shows a proposal of prevention measures in different hospital settings providing care to cardiovascular patients.

The operating room and the catheterization/electrophysiology labs

Case study 3: A 65-year-old male was admitted for a STEMI code on 11 March. An urgent angiography showed severe stenosis of the proximal left anterior descending artery, which was treated percutaneously with a drug-eluting stent in the haemodynamic laboratory. On 19 March, he developed a moderate COVID-19 pneumonia. Contact tracing revealed 20 contacts but no secondary cases in coronary and cardiology units. The patient was successfully treated and discharged to a convalescence centre 14 days later. However, the three staff members of the haemodynamic laboratory developed COVID-19.

Takeaway: When urgent screening for SARS-CoV-2 infection cannot be performed, appropriate PPE must be used. In addition, acute coronary syndrome could be indirectly related to COVID-19.

An operating room with a negative pressure setting located as far away as possible from other operating rooms, with separate access,

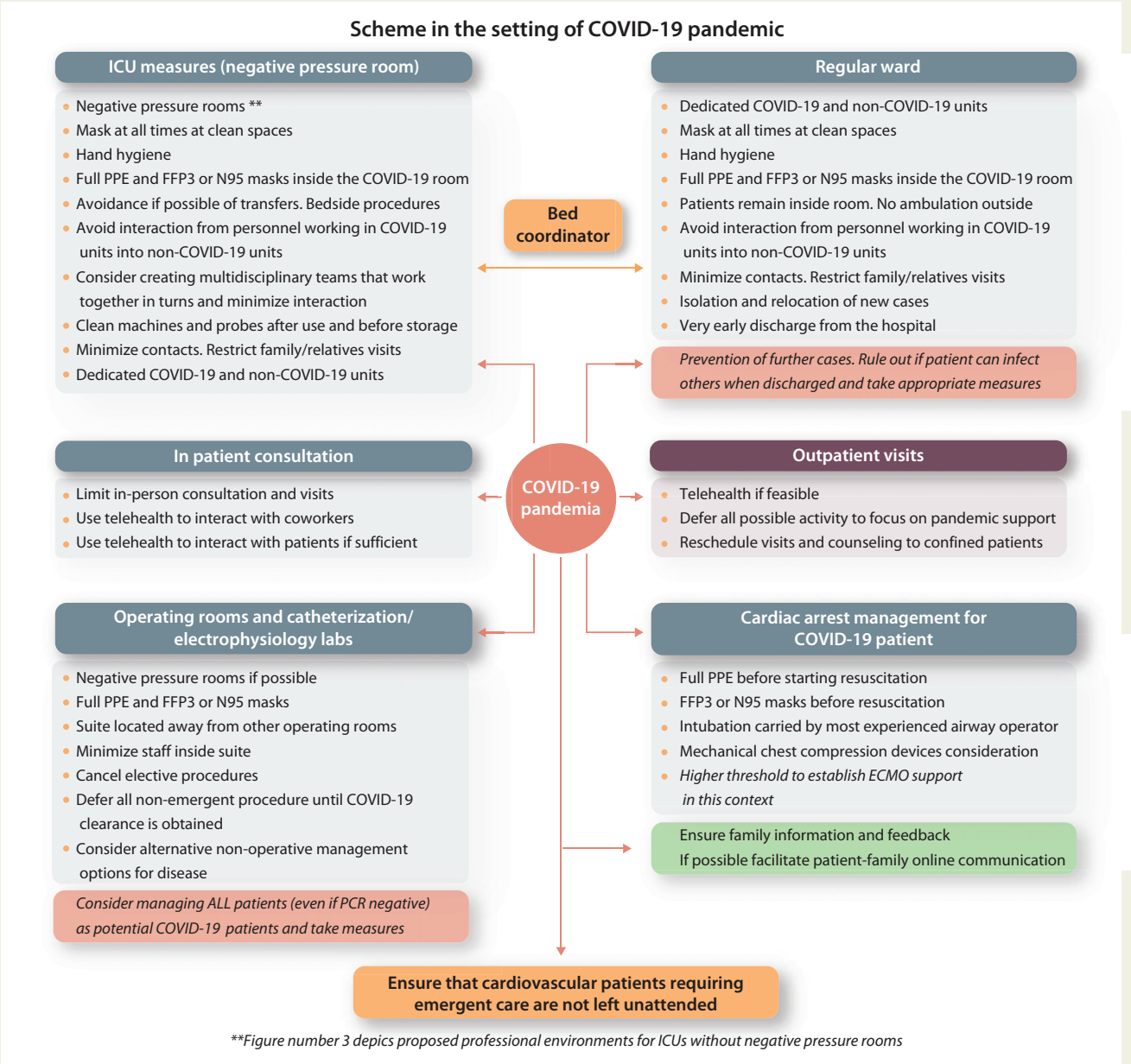

Figure 3 Proposed scheme of prevention measures in different settings involving cardiovascular patients during the COVID-19 pandemic. ECMO, extracorporeal membrane oxygenation; PPE, personal protective equipment.

is recommended for suspected or confirmed COVID-19 patients.[86] Full PPE should be worn in compliance with current recommendations (including an N95 or FFP3 mask). If negative pressure environments are not available, the operating room doors should be kept closed to avoid airborne spreading of the virus. This applies to any interventional cardiovascular procedure. However, specific problems can be encountered in cardiac surgeries requiring surgical field magnification loupes that may compromise compliance with protective recommendations. In this scenario, other forms of myocardial revascularization may be preferable.

For catheterization suites, the conventional emergent transfer for diagnostic/therapeutic purposes has been questioned during the pandemic situation, and proposals to screen every single patient for COVID-19, regardless of delay in therapy, have been adopted by some practitioners.[87,88] The consensus is that percutaneous coronary intervention (PCI) remains the first option except for cases of severe COVID-19. This strategy may apply to any non-emergent cardiac surgery. The need to individualize decisions gains relevance in this context.[89,90] When in doubt, if the situation does not allow for confirmatory tests, the recommendation should be to proceed with full PPE and adopt all strategies as when dealing with a confirmed COVID-19 patient. Any other non-urgent/emergent procedure which merits full investigation and systematic screening prior to invasive procedures may ultimately be indicated to prevent some of the exposed clinical issues here.

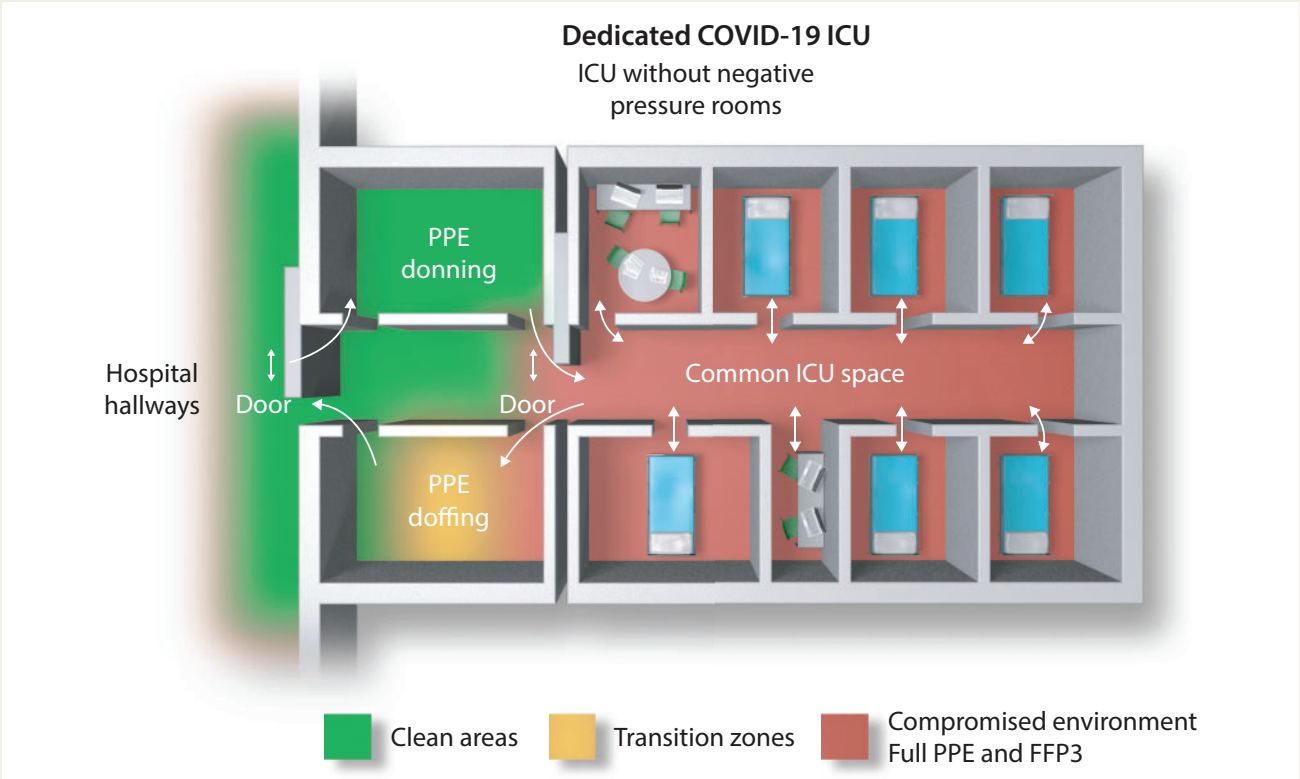

Figure 4 Proposed organization of an ICU during the COVID-19 pandemic (see text for explanation). FFP3, filtering facepiece protection 3; PPE, personal protective equipment.

Special considerations for management of cardiovascular emergencies in confirmed or suspected COVID-19 patients

While it is crucial that prevention measures, especially in the ICU, do not compromise appropriate monitoring and timely therapeutic action, it is also of outstanding importance to avoid healthcare workers and other patients being infected due to the lack of appropriate actions taken during a cardiovascular emergency. Prevention and control of COVID-19 transmission should be adopted as the highest priority, including self-protection of medical staff.[82] If possible, invasive procedures should be replaced by more conservative ones while aiming for the best possible patient outcomes. Also, minimizing transfers within the hospital is recommended, and therefore all tests and procedures should be performed at the bedside if feasible. *Figure 4* shows a proposed organization of ICU areas to minimize spread of the virus among patients and staff.

During a cardiac arrest, PPE needs to be worn by all members of the resuscitation team. Prolonged facemask ventilation should be avoided to decrease the amount of aerosol generation. Consideration should be given to using automated chest compression devices to minimize contact. Intubation and chest compressions should be delayed until fully equipped personnel with PPE become ready to interact safely.[89]

Burdens of operability in a COVID-19 environment

The burdens of cardiac operability, procedural choice, and best resource allocation during a pandemic outbreak may remain debatable and are under investigation. A delay in emergent life-threatening conditions requiring cardiac surgery is not justified unless restrictive criteria (limitation to ICU acceptance) are applied to the entire healthcare system. Fortunately, the majority of patients with severe forms of heart disease may tolerate a delay of weeks to months under best medical treatment. Estimates of hospital occupancy and availability of resources need to be frequently revisited with the intention of reallocating these patients into the surgical schedule as soon as possible. For urgent conditions that cannot be delayed (most frequently unstable coronary disease), alternative modalities of treatment may be given priority despite different existing guideline recommendations. In the transplant arena and due to a perceived increased risk of complications in such patients, it may be justifiable to accept a 'programme lock down' period for elective heart transplantation.

Allocation of resources and service preservation in cardiovascular departments

Care for non-COVID-19 patients must continue despite the extreme pressures to which many European healthcare systems have been exposed. Cardiac surgery departments have a responsibility to their patients that may have been compromised, in a large number of practices, during the pandemic. This may have happened as a result of reallocation of hospital resources or due to maintaining unaltered practices in healthcare environments that were not safe, resulting in an incremental risk of surgery. Preservation of dedicated teams for

highly specialized practices could make sense as long as the pandemic situation does not force the system to use all its assets. The proposed clustered or high-intensity staffing models could maintain operability throughout part of the crisis if containment measures towards the COVID-19 pandemic does not collapse the healthcare system.[91] Such teams would be designed to cluster an attending physician, a cardiovascular resident or fellow, two to three nurses, and anesthesiologists. The teams would remain available and together until one member becomes infected (or under suspicion of infection). The workload would be distributed to a number of clustered teams to provide a full operative service. Maintaining certain physicians with a particular unique skill set (e.g. interventional cardiologists and cardiac surgeons) working away from the frontline services may be reasonable when the system can still compensate for their absence without imposing a downgrade of care to COVID-19 patients. In the event the system becomes overwhelmed due to a lack of manpower, such physicians should be prepared to commit the full spectrum of their skills and capabilities to mitigate the consequences of a pandemic.[92]

Reintroducing cardiovascular services after COVID-19

Once the peak of COVID-19 is overcome in a particular setting, the safe reintroduction of cardiovascular services requires close collaboration between public health officials and health systems. It is to be noted that different invasive procedures and diagnostic tests might be at different levels of re-escalation within a given region depending on local COVID-19 penetrance and infrastructure requirements. The process of reincorporating cardiovascular services is dynamic and the capacity to manage a potential second wave of COVID-19 should be maintained while there is still a risk of a second surge.[93]

Conclusions

The COVID-19 pandemic is largely and rapidly affecting daily clinical practice, and cardiologists and cardiovascular surgeons are not exempt. Being aware of and updated on how SARS-CoV-2 is transmitted, how it can be prevented, and who should be screened for infection is currently crucial for the exercise of professional duties. Also, all clinicians should be able to identify early clinical manifestations of COVID-19, including cardiovascular complications, and therapeutic options as well as potential interactions with cardiovascular drugs should be well known.

From a professional standpoint it seems wise to build a strong, straightforward, coordinated, and anticipated response during the initial phase of disease locally. Early implementation of exponential preventive measures by means of universal use of masks, minimization of personnel/patient and co-worker interaction, along with rescheduling non-urgent consultations and surgeries, may facilitate better institutional preparation for the peak caseload.

Alignment of regulatory bodies, healthcare institutions, clinical services, and individual professional initiatives in the right direction could allow avoidance of unnecessary mortality and complications related to severe forms of COVID-19 in the general population and early after cardiovascular procedures.

Author contributions

All the authors listed in the contributors' affiliations meet the ICMJE Authorship Criteria; that is, they substantially contributed to conception and design, acquisition of data, drafting of the article, critical revision, and final approval of the manuscript.

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